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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HM12/1123

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GAMBEL, P	20

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/7/99

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1, 5-10, 13-18, 21-31 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1, 5-10, 13-18, 21-31 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Claims 1, 5-10, 13-18, 21-31 are pending

Claim 2-4, 11, 12, 19 an 20 have been canceled previously.

2. Applicant's Brief on Appeal, filed 9/7/99 (Paper No. 19), is acknowledged.

Applicant argues in the Brief on Appeal, filed 9/7/99 (Paper No. 19), that the pending claims are entitled to a priority date based upon USSN 07/958,248, filed 10/8/92.

The following issues of priority of the instant claims are addressed
1, 6, 10, 14, 18, 26 and 27
A) Claims 1, 6, 10, 14, 18, 26 and 27.
TNFα

Applicant relies upon pages 8, 10, and 11 of USSN 07/958,248 to support treating autoimmune diseases inflammatory diseases, including Crohn's disease and rheumatoid arthritis, with anti-TNF antibodies and that methotrexate can be used in conjunction with anti-TNF antibodies.

Upon reconsideration of a review of the priority application USSN 07/958,248, filed 10/8/92 in conjunction with applicant's arguments; the priority of instant claims 1, 6, 10, 14, 18, 26 and 27 is deemed to the be the filing date of USSN 07/958,248, filed 10/8/92. In conjunction with applicant's arguments and Exhibit 1 (Abbas et al. Cellular and Molecular Immunology, 3rd Edition, 1997, page 258); Paul (Fundamental Immunology, Third Edition, 1993; pages 807-812, particularly Table 2) supports applicant's reliance on the disclosure of TNF in USSN 07/958,248 to be TNFα.

Due to the inclusion of Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 318; see 1449, #AR3), Pascalis et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 319; see 1449, #AR3) in the rejection under 35 USC 103 of record; a New Grounds of Rejection is set forth relying upon the references of record but not including Cohen et al. and Pascalis et al. as it applies to instant claims 1, 6, 10, 14, 18, 26 and 27. Cohen et al. and Pascalis et al. had been provided as further evidence of the obviousness of the claimed invention and in the previous position that these claims did not receive priority due to the recitation of "TNFα".

B) Claims 5 (and dependent claims 7-9) and Claim 13 (and dependent claims 14-17) and Claims 21 (and dependent claims 22-25)
Multiple Doses

Applicant's reliance on parent USSN 07/958,248 for the priority of all of the pending claims have been fully considered but not found convincing essentially for the reasons of record.

Applicant argues that page 4, lines 4-6 and page 9, lines 24-26 of parent USSN 07/958,248 discloses that "administration can be in the form of a single dose or a series of doses separated by interference of days or weeks". Applicant asserts that the ordinary artisan would reasonably interpret this disclosure to mean "multiple doses".

In contrast to applicant's assertions, "multiple doses" encompasses more than that the "administration can be in the form of a single dose or a series of doses separated by interference of days or weeks". For example, "multiple doses" could occur within a day (e.g less than days and weeks) or could be provided with other reagents/treatments or could be provided as a preconditioning or postconditioning regimen. The scope or metes and bounds of "multiple doses" as currently claimed is broader and different from that disclosed in USSN 07/958,248.

Therefore, "multiple doses" receives the priority date to USSN 08/607,419, filed 2/28/96.

Applicant's arguments are not found persuasive.

C) Claims 7-8, 15-17 and 23-25 and 28-30:
"One or more epitopes included in amino acid residues of about 87-108 (SEQ ID NO:1) or about 59-80 (SEQ ID NO: 2) of hTNFα" and "cA2"
Incorporation by reference to USSN 07/943,852 in parent USSN 07/958,248

Applicant's reliance on parent USSN 07/958,248 for the priority of all of the pending claims have been fully considered but not found convincing essentially for the reasons of record.

Applicant asserts that page 8, line 16-17 of USSN 07/958,248 which incorporates by reference to USSN 07/943,852, filed 9/11/92; which is asserted to disclose anti-TNF antibodies encompassing the limitations of instant claims 7-9, 15-17, 23-25 and 28-30.

Incorporation by reference

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United states or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

It is noted that USSN 07/943,852 was not listed a priority document of the instant application nor as a priority document of the priority application of the instant family of continuation-in-part applications.

It is noted that USSN 07/943,852 has been abandoned

It is noted that USSN 07/943,852 is a priority document of the U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195 and U.S. Patent No. 5,919,452.
Le et al., U.S. Patent No. 5,656,27 has been used as a prior art reference in the instant application.

It is noted that page 8, line 16-17 of USSN 07/958,248, which incorporated by reference to USSN 07/943,852, filed 9/11/92, had been canceled by applicant's amendment.

Also, it is noted that the "claimed limitations" relied upon from USSN 07/943,852 have not been incorporated into the priority USSN 07/943,852 application itself nor in priority USSN 08/403,785, filed 5/3/95.

The current limitations drawn to anti-TNF antibodies encompassing the limitations of instant claims 7-9, 15-17, 23-25 and 28-30 do not have written support until parent USSN 08/607,419 and therefore receive priority to USSN 08/607,419, filed 2/28/96.

Applicant's arguments are not found persuasive.

D) Claim 31:
TNF antagonists

Applicant argues that page 11, lines 1-6 of USSN 07/958,248 describes the use of other agents which interfere with TNF, TNF receptor signaling or TNF synthesis (TNF antagonists).

However, page 11, lines 1-6 of USSN 07/958,248 discloses "inflammatory mediators include agents interfering with TNF, such as anti-TNF antibody, soluble TNF-R (monomeric, IgG fusion proteins, etc.) Or blocking peptides and small molecules interfering with TNF receptor signaling or with TNF synthesis such as pentoxyfilline and thalidomide".

However, pages 12-13 of the instant specification defines "tumor necrosis factor antagonists" as ones which "decrease, blocks, inhibit abrogate or interferes with TNF activity in vivo and provides examples not disclosed in page 11, lines 1-6 of USSN 07/958,248.

It appears that the definition as well as the scope and metes of bounds of the "TNF antagonists" as disclosed in the instant specification differ from the "agents that interfere with TNF, TNF receptor signaling or TNF synthesis" as disclosed in page 11, lines 1-6 of USSN 07/958,248.

The current limitation of "TNF antagonists" does not have written support until parent USSN 08/607,419 and therefore receive priority to USSN 08/607,419, filed 2/28/96.

Applicant's arguments are not found persuasive.

E) Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed Brief on Appeal, filed 9/7/99 (Paper No. 19).
The rejections and art of record can be found in the previous Office Actions (Paper Nos. 6/15).

4. Claims 1-3, 5-9 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention to use the combination of anti-TNF antibodies and methotrexate encompassed by the claimed methods to treat any autoimmune or inflammatory disease encompassed by the claimed methods essentially for the reasons of record set forth in the last Office Action (Paper No. 6).

As pointed out in the previously; although in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions that experienced in the human immunoregulatory diseases such as the acute and chronic immune diseases, autoimmune diseases, inflammatory diseases and neurodegenerative diseases targeted by the claimed invention. In human diseases, patients are treated generally after the onset of disease and not prior to disease.

Natanson et al. (Ann Int Med., 1994) teach that anti-TNF was not beneficial in sepsis and septic shock and that targeting TNF could be harmful (see Anticytokine Therapies).

In addition to limitation of anti-TNF antibody treatment broadly encompassing treating any autoimmunity or inflammatory diseases; there is insufficient direction and guidance to apply the highly toxic reagent methotrexate in the claimed methods to broadly treat any autoimmunity or inflammatory disease. It has been well known to those skilled in the art that methotrexate causes numerous specific toxicities encompassing drug interactions, delayed absorption, elimination and renal failure (see pages 308-309 of Manual of Medical Therapeutics, 25th Edition 1986). While there is objective evidence that methotrexate has been used in rheumatoid arthritis and Crohn's disease (as well as cancer, which is not claimed); there is insufficient guidance and direction to treat any autoimmunity or inflammatory diseases wherein methotrexate is provided as a therapeutic drug.

Therefore, it is not clear that the skilled artisan could predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with TNF specific antibody and methotrexate. It is important to note that there are distinct differences in the cytokine requirements for particular types of inflammation Applicant has not provided sufficient information or nexus information a priori that establishes the efficacy of the claimed invention for the treatment of any TNF-mediated disease by administering TNF-specific antibody and methotrexate. The specification does not teach how to extrapolate data obtained from anti-TNFα and methotrexate on arthritis to the development of effective in vivo human therapeutic methods and compositions for any TNF-mediated diseases, commensurate in scope with the claimed invention which applies combination therapy.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy and methotrexate commensurate in scope with the claimed methods and compositions, undue experimentation would be required to practice the claimed methods and compositions with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and compositions and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting any autoimmune or inflammatory disease.

Applicant's arguments set forth in the Brief on Appeal, filed 9/7/99 (Paper No. 19) have been fully considered but are not found convincing essentially for the reasons of record.

Again, applicant relies upon the disclosure of a number of autoimmune and inflammatory diseases and the exemplification of cA2 in patients with active rheumatoid arthritis in the instant application as well as Crohn's disease in Le et al. (U.S. Patent No. 5,656,272) to provide reasonable expectation of success that the claimed methods would work in the same manner for other autoimmune and inflammatory diseases, known to be mediated by TNFα

While applicant appears to acknowledge that Natanson et al. (Ann. Int. Med. 120: 771-783, 1994) discloses the limitation of targeting TNF-mediated disease as it applies to sepsis; applicant relies upon setting forth categories of diseases in which TNFα has been implicated, as disclosed on pages 3 and 8-99 of the specification. Here, applicant appears to exclude Item B, for infections encompassing sepsis, Item D for neurodegenerative diseases and Item E for malignancies.

However, the specification discloses that these various categories "include" certain pathologies but "are not limited to" the particular pathologies disclosed. Also, various diseases encompassed in the different categories have or appear to have an infectious agent involved either in stimulating or exacerbating the various diseases in the various categories. Therefore, the various categories of TNF-mediated disease are not mutually exclusive.

In supporting the unpredictability of relying upon treating one disease to predict treating another disease; Debets et al. (Immunology Today 15: 455-458, 1994) discloses that the double-edged sword paradigm of soluble receptors also applies to anticytokine antibodies when relying upon the potential therapeutic use of cytokine antagonists (see entire document, including page 457, column 3, Anticytokine autoantibodies).

As pointed out previously there are a number of diseases characterized by the presence or association of TNFα; however it would not have been predictable to the skilled artisan to treat the breadth of inflammatory diseases via a particular mediator or in the instant invention via anti-TNFα antibody and methotrexate.

Again, this rejection does not apply to the use of anti-TNFα antibody and methotrexate in treating rheumatoid arthritis and Crohn's disease, but rather to the scope of targeted diseases based upon the limited examples of rheumatoid arthritis and Crohn's disease.

Applicant's arguments are not found persuasive, particularly as it applies to "inflammatory diseases" and particularly as it applies to the "combination of anti-TNFα antibody and methotrexate", commensurate in scope with the claimed invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 5-10, 13-18, 21-31 are rejected under 35 U.S.C. § 102(e) as being anticipated by each of Le et al. (U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195 and U.S. Patent No. 5,919,452).

For convenience, each Le et al. Patent is listed, given that the claimed methods are encompassed by the instant invention. Given that the priority and the disclosure of each Le et al. Is the same; each Le et al. Patent is set forth in this 102(e) rejection. However, the 102(e) rejection is based upon each Le et al. Patent individually and not applied to their combination.

Also, upon reviewing the priority of the instant claims and the disclosures of the prior art and an updated search; it appears that the Le et al. Patents disclose the combination of anti-TNFα antibodies including the cA2 specificities in combination with methotrexate. Therefore, a New Grounds of Rejection has been set forth herein.

The Le et al. Patents teach the use of TNF-specific antagonists including the instant cA2 antibody to treat inflammatory diseases including arthritis, Crohn's pathology and ulcerative colitis (see entire documents; for example, see '272, including Therapeutic Administration in columns 35-38, Examples XX-XXIII in columns 58-79). It is noted that the clinical patients targeted by the cA2 treatment in the clinical trials taught by Le et al. were refractory to disease modifying anti-rheumatic drugs (DMARD); however it is also noted that methotrexate was such a DMARD (see Example XXII for example). Also, Le et al. teaches that the anti-TNF peptides and/or mAbs of their invention can be administered either as individual therapeutic agents of in combination with other therapeutic agents (for example, see '272; see column 35, lines 25-32). Le et al. teach the use of conjugating immunoreceptors with methotrexate (for example see '272; see column 23, paragraph 1 and column 37, paragraph 1).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods for treating autoimmune and inflammatory diseases with TNF-specific antagonists in combination with other known reagents including methotrexate.

8. Claims 5 and 31 are rejected under 35 U.S.C. § 102(e) as being anticipated Feldmann et al. (U.S. Patent No. 5,741,488). Feldmann et al. teaches the use TNFα-specific antibodies as well as agents interfering with TNF, such as anti-TNF antibody, soluble TNF-R can be administered in combination with methotrexate in a series of doses separated by days or weeks (see columns 3 and 5) for the treatment of various autoimmune and inflammatory conditions (see entire document). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods for treating autoimmune and inflammatory diseases with TNF-specific antagonists in combination with other known reagents including methotrexate

As pointed out above, claims 5 and 31 do not receive the priority of USSN 07/958,248, filed 10/8/92. Feldmann et al. (U.S. Patent No. 5,741,488) is done by another.

9. Claims 1, 5-10, 13-18, 21-31 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter.

Given applicant's assertions set forth in the Brief on Appeal, filed 9/7/99 (Paper No. 19), which asserts priority for the instant claims back to priority applications USSN 07/958,248 and USSN 08/403,785, which incorporates by reference to USSN 07/943,852; it is not clear that named inventive entity Feldmann and Maini alone are the sole inventors of the claimed invention.

For example, U.S. Patent No. 5,741,488, filed as USSN 08/403,785, which also claims priority to USSN 07/958,248; lists Feldmann, Maini and Williams. Williams is not listed as an inventor in the instant application.

It is noted that the incorporation by reference application USSN 07/943,852 is a priority document of the U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195 and U.S. Patent No. 5,919,452. These U.S. Patents list Le, Vilcek, Daddona, Ghrayeb Knight and Siegel as inventors, none of which are in common with the instant inventive entity.

These U.S. Patents as well as applicant's reliance upon priority documents which are common to these U.S. Patents presents an ambiguity with regard to inventorship because the named inventive entities differ from those listed as inventors in the instant application.

Because of this ambiguity, it is incumbent on applicants to provide a satisfactory showing which would lead to a reasonable conclusion that named applicants alone are the inventors of the claimed invention. To resolve the ambiguity, applicants may file declarations by the non-applicant co-authors of the references disclaiming the invention or a declaration by applicant setting forth the facts which provide an explanation as to why the non-applicant members of the inventive entities of the U.S. Patents are not inventors herein.

10. Claims 1, 5-10, 13-18, 21-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Le et al. (U.S. Patent No. 5,656,272; of record) AND/OR Le et al. (U.S. Patent No. 5,698,195) AND/OR Le et al. (U.S. Patent No. 5,919,452)
AND Aggarwal et al. (U.S. Patent No. 5,672,347; of record)
in view of Barrera et al. (Cytokine, 1991) and Kozarek et al. (Ann. Int. Med., 1989) of Markowitz et al. (J Ped. Gastroenterology and Nutrition, 1991) essentially for the reasons of record set forth in Paper Nos. 6/15).

As pointed out above, Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 318; see 1449, #AR3), Pascalis et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 319; see 1449, #AR3); have been withdrawn; given that claims 1, 6, 10, 14, 18, 26 and 27 have a priority date back to priority USSN 08/07/958,248, filed 10/8/92. Cohen et al. And Pascalis et al. Had been added to provide further evidence that methotrexate had been used in treating rheumatoid arthritis and Crohn's disease. Such teachings can be found in the prior art set forth herein.

Le et al. (U.S. Patent No. 5,698,195) and Le et al. (U.S. Patent No. 5,919,452) have been added, given that the claimed inventions in these U.S. Patents read on the targeted diseases encompassed by the claimed invention. Their teachings are the same as of Le et al. U.S. Patent No. 5,656,272; already of record.

The Le et al. Patents teach the use of TNF-specific antagonists including the instant cA2 antibody to treat inflammatory diseases including arthritis, Crohn's pathology and ulcerative colitis (see entire documents; for example, see '272, including Therapeutic Administration in columns 35-38, Examples XX-XXIII in columns 58-79). It is noted that the clinical patients targeted by the cA2 treatment in the clinical trials taught by Le et al. were refractory to disease modifying anti-rheumatic drugs (DMARD); however it is also noted that methotrexate was such a DMARD (see Example XXII for example). Even though the particular patient populations employed in the referenced clinical trials were refractory to standard DMARD including methotrexate treatment, it would have been obvious to the ordinary artisan that the combination of standard methotrexate treatment in combination with a highly effective TNF antagonist such as cA2 would be similarly effective for treating patients with inflammatory conditions already being treated with standard methotrexate as well as a TNF antagonist. Also, Le et al. teaches that the anti-TNF peptides and/or mAbs of their invention can be administered either as individual therapeutic agents of in combination with other therapeutic agents (for example, see '272; see column 35, lines 25-32).

Aggarwal et al. teaches the use of TNF antagonists including TNF-α-specific antibodies and analogues to treat various inflammatory conditions including arthritis and Crohn's disease (see entire document, including overlapping paragraph of columns 6-7). Aggarwal et al. also teach that the TNF antagonist can be administered in conjunction with other anti-inflammatory agents used in or prosed for the treatment of individual inflammatory conditions as appropriate (column 7, lines 60-67). Here, TNF antagonists when employed together with other anti-inflammatory agents, these agents may be employed in lesser dosages than when used alone. Although this reference does not teach the particular cA2 specificity per se, Aggarwal et al. clearly teaches the use of TNF-α antagonist to treat inflammatory conditions encompassed by the claimed invention. In addition, Aggarwal et al. teaches the art known advantages of combination therapy, wherein the ordinary artisan can take advantage of two or more therapeutic agents to treat the same disease and that in instances, this combination permits one agent to be used in lesser amounts, thereby counteracting any toxic effects,

Barrera et al. teaches the use of methotrexate including suppressing the production of TNF in arthritic patients (see Abstract).

Kozarek et al. teach the use of methotrexate as an anti-inflammatory agent on inflammatory bowel disease (see entire document).

Markowitz et al. teaches targeting TNF (page 413) and the use of methotrexate (page 421) in the treatment of inflammatory bowel diseases (see entire document)

Therefore, the prior art taught the claimed TNF-specific antagonists and methotrexate as well as their combinations; therefore it would have been obvious to one of ordinary skill at the time the invention was made to make various combinations of said anti-inflammatory antagonists to achieve the same desired goals in treating arthritis and Crohn's disease. diminished TNF activity to suit the nature of the therapeutic regimen. The combination of references provide an expectation of success in combining various compositions to form a third composition to most effectively induce the appropriate immunosuppression for a targeted condition.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 5, 7-10, 13, 15-18, 21-25 and 28-31 are rejected under 35 U.S.C. § 103 as being unpatentable over
Le et al. (U.S. Patent No. 5,656,272; of record) AND/OR Le et al. (U.S. Patent No. 5,698,195) AND/OR Le et al. (U.S. Patent No. 5,919,452)
AND Aggarwal et al. (U.S. Patent No. 5,672,347; of record)
in view of Barrera et al. (Cytokine, 1991) and Kozarek et al. (Ann. Int. Med., 1989) of Markowitz et al. (J Ped. Gastroenterology and Nutrition, 1991),
as applied to claims 1, 5-10, 13-18, 21-31 above and in further view and evidence of Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 318; see 1449, #AR3), Pascalis et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 319; see 1449, #AR3);

Le et al. (U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195; U.S. Patent No. 5,919,452), Aggarwal et al., Barrera et al., Kozarek et al. and Markowitz et al. Have all been taught above.
As pointed out above, Cohen et al. and Pascalis et al. Have been added to provide further evidence of teaching the use of methotrexate to treat refractory rheumatoid arthritis (see Abstracts)

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo.

It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 5, 7-10, 13, 15-18, 21-25 and 28-31 are rejected under 35 U.S.C. § 103 as being unpatentable over
Le et al. (U.S. Patent No. 5,656,272; of record) AND/OR Le et al. (U.S. Patent No. 5,698,195) and Le et al. (U.S. Patent No. 5,919,452)
AND Aggarwal et al. (U.S. Patent No. 5,672,347; of record)
AND/OR
Feldmann et al. (U.S. Patent No. 5,741,488)
in view of Barrera et al. (Cytokine, 1991) and Kozarek et al. (Ann. Int. Med., 1989) of Markowitz et al. (J Ped. Gastroenterology and Nutrition, 1991),
as applied to claims 1, 5-10, 13-18, 21-31 above
OR in further view and evidence of Cohen et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 318; see 1449, #AR3), Pascalis et al. (Rev. Esp. Rheumatol., 20 Suppl 1:148 (1993), Abstract 319; see 1449, #AR3);

As indicated above and given the lack of priority of the instant application to USSN 08/07/958,248, filed 10/8/92 and that Feldmann et al. is done by another; Feldman has been applied as a primary reference against the instant claims.

Feldmann et al. Teaches the use of anti-TNFα antibodies in conjunction with methotrexate (column 5, paragraph 5) to treat autoimmune and inflammatory diseases (column 6, paragraph 2), including rheumatoid arthritis and Crohn's disease as well as the use of chimeric antibodies (columns 3-4) and modes of administration (column 5, paragraphs 1-4) encompassed by the claimed invention (see entire document).

Le et al. (U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195; U.S. Patent No. 5,919,452); Aggarwal et al.; Barrera et al.; Kozarek et al. and Markowitz et al.
OR in further view and evidence of Cohen et al. and Pascalis et al. Have all been taught above

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo.

It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Applicant's arguments, set forth in the Brief on Appeal, filed 9/7/99 (Paper No. 19) 6/10/98 (Paper No. 13), have been fully considered but are not found convincing.

Applicant's arguments and the examiner's rebuttal are essentially the same as of record.
A more thorough review of applicant's arguments and the examiner's rebuttal of record can be found in Paper No. 15.

Again, applicant's reliance on the asserted unexpected results of the combination of anti-TNFα antibody and methotrexate over each agent alone as disclosed in Examples 1 and 2 of the instant specification is acknowledged. Applicant asserts that the magnitude of these results in the treatment of autoimmune or inflammatory disease could not have reasonably predicted from the cited references, as illustrated in the instant Examples. Applicant argues that there is nothing in the record that the ordinary artisan would reasonably conclude that such a dramatic effect would be expected by combination therapy with methotrexate and anti-TNFα antibody

In contrast to applicant's assertions, consideration of the disclosed results were considered .

It has been acknowledged that applicant has asserted that the unexpected result that combination therapy with methotrexate and anti-TNFα antibody produced a rapid and sustained reduction in the signs and symptoms of the treated autoimmune disease, namely rheumatoid arthritis (Example 2). Applicant asserts that the combination of methotrexate and anti-TNFα produced markedly superior results to that the results obtained with each agent alone, particularly at low doses of methotrexate. Applicant also asserts that significant improvement of the combination therapy was observed even in comparison to where optimal dosages of anti-TNFα antibody were administered alone (Example 1). Applicant states that is now well settled that significant improvements can rebut a prima facie case of obviousness. See In re Kollman, 201 USPQ 193 (CCPA 1979) and MPEP 716.02.

Applicant argues that the cited references alone of in combination do not provide an expectation of success or being effective in treating an autoimmune or inflammatory disease in an individual comprising co-administering methotrexate and an anti-TNFα antibody (or TNF anti-TNFα antibody antagonist).

Also, applicant's arguments rely, in large part, to the asserted synergistic effects disclosed in the instant examples. Applicant's asserted synergistic effects are based upon the comparison of each therapeutic modality used separately. Also, it has been noted that such effects were observed with certain patient populations with certain dosing. The putative synergistic effects relate to a particular multiple dose regiment of based upon cA2 and methotrexate therapy in rheumatoid arthritis patients whose disease is incompletely controlled by methotrexate (see page 62, paragraph 3 and page 66, paragraph 3 of the specification). Such particular patient populations and particular dosing regimens are not claimed. Also, it is noted that such effects observed with certain patient populations with certain dosing regimens does not discount the well known use and expectation of success in combining therapeutic agents to treat diseases.

As noted previously, Borigini et al. (Balliere's Clinical Rheumatology, 1995) (1449) discloses in a review on combination therapy that it was art known that conventional therapies had their limitations, particularly in certain patient populations and that the ordinary artisan was motivated with an expectation of success in combining conventional therapies with agents that inhibit specific events in inflammation (see entire document).

As pointed out previously, the prior art did teach the art known advantages of combination therapy, wherein the ordinary artisan can take advantage of two or more therapeutic agents to treat the same disease and that in instances, this combination permits one agent to be used in lesser amounts, thereby counteracting any toxic effects. Also, the prior art did teach efficacy of anti-TNFα antibody in treating patients treated with conventional therapy at the time the invention was made. The prior art also taught the use of anti-TNFα antibody in patients who were resistant to conventional therapy with methotrexate. Therefore it appears that the prior art and the instant Examples rely on showing the efficacy of anti-TNFα in similar patient populations and that treatment with an anti-TNFα antibody such as cA2 in an adjunctive and/or concomitant therapy to conventional therapy was expected to be an important and efficacious therapeutic approach for treating patients. Also in contrast to applicant's assertion, the concomitant use of immunosuppression with antibody therapy was expected to reduce the immunogenicity of therapeutic antibodies and to increase bioavailability of such antibodies at the time the invention was made.

Applicant's arguments concerning the secondary references are acknowledged, however the combination of prior art references do provide the expectation of success in combining methotrexate and an anti-TNFα antibody in treating certain inflammatory or autoimmune diseases encompassed by the claimed methods for the reasons of record.

In contrast to applicant's arguments, given the prior art of record, the ordinary artisan would reasonably conclude a therapeutic effect would be expected by combination therapy with methotrexate and anti-TNFα antibody.

Applicant's reliance on certain therapeutic effects with certain dosing does not obviate the motivation and expectation of success in treating autoimmune or inflammatory disease with a highly effective anti-TNFα antibody together with conventional therapies such as methotrexate, as evidenced of record. such as anti-TNF. Again, it is noted that the prior art recognized the same or similar advantages of treating the same or similar patient populations to achieve the same or similar therapeutic effects with the same combination of antiinflammatory agents, encompassed by the claimed methods. That certain patient populations were resistant to conventional therapy does not discount the use of said conventional therapy in combination with other effective agents to achieve a desired end result. Targeting different elements of an inflammatory response as well as the expectation of success with such combination therapy was known and practiced at the time the invention was made by the ordinary artisan.

The nonobviousness of a broader claim can be supported by evidence based on unexpected results from testing a species contained within the claim if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof to the broader claim. In re Kollman 201 USPQ 193 (CCPA 1979). Here, however, given the unpredictability associated with synergistic effects of treating autoimmune or inflammatory diseases with the combination of TNFα-specific antagonists and methotrexate; it does not appear that the specification provides sufficient objective evidence to extend unexpected results showing contained herein based upon the asserted synergistic effects of this combination therapy in rheumatoid arthritis patients who were resistant to conventional therapy with methotrexate.

It appears that applicant's assertion of synergistic results based upon by the limited clinical results rheumatoid arthritis patients who were resistant to conventional therapy with methotrexate in the instant application appears inconsistent with applicant's assertion of priority; wherein USSN 07/958,248 simply disclosed that other anti-inflammatory agents such as methotrexate can be administered in conjunction with anti-TNF antibodies. It appears that applicant's priority documents recognized the known and standard practice of combination therapies, including the combination of agents, each known to have a therapeutic role in treating the same disease.

Applicant's reliance on unexpected results do not overcome clear and convincing evidence of obviousness. Also see Richardson-Vicks Inc. v. Upjohn Co., 44 USPQ2d 1181 (CAFC 1997)

Applicant's arguments are not found persuasive.

14. Given the abandonment of USSN 08/607,419; the previous rejection under the judicially created doctrine of obviousness-type double patenting has been obviated.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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November 22, 1999
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